



Ali, M. S., Ernst, M., Robinson, D. E., Caskey, F., Arden, N. K., Ben-Shlomo, Y., Nybo, M., Rubin, K. H., Judge, A., Cooper, C., Javaid, M. K., Hermann, A. P., & Prieto-Alhambra, D. (2020). Alendronate use and bone mineral density gains in women with moderate-severe (stages 3B-5) chronic kidney disease: an open cohort multivariable and propensity score analysis from Funen, Denmark. *Archives of Osteoporosis*, 15(1), [81 (2020) ]. <https://doi.org/10.1007/s11657-020-00746-z>

Peer reviewed version

Link to published version (if available):  
[10.1007/s11657-020-00746-z](https://doi.org/10.1007/s11657-020-00746-z)

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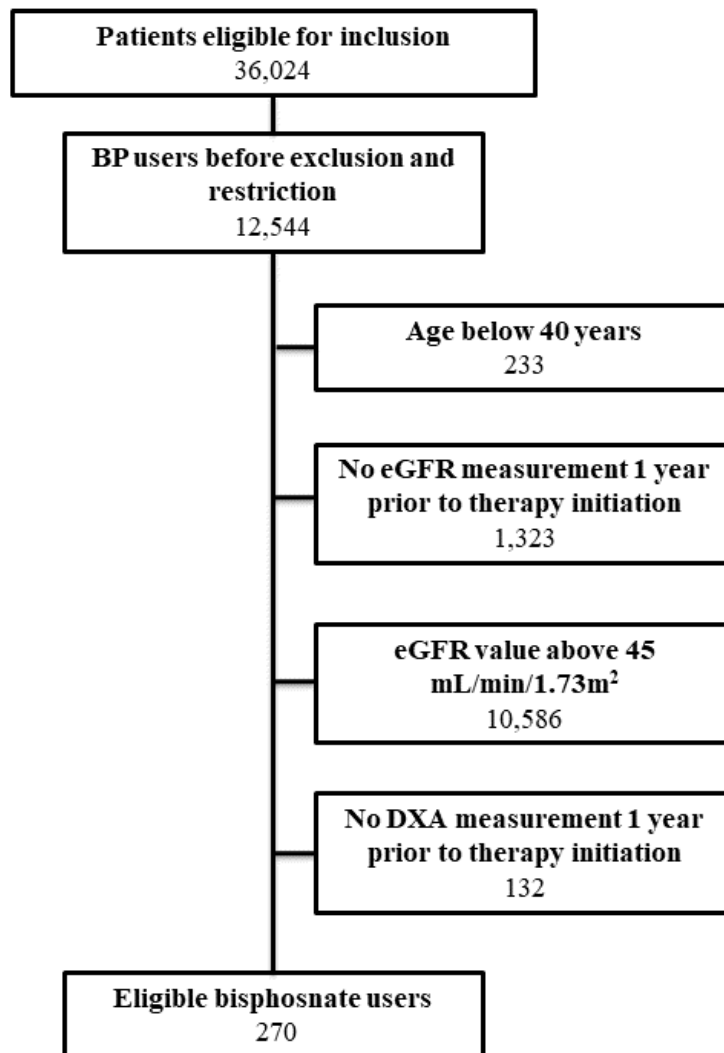
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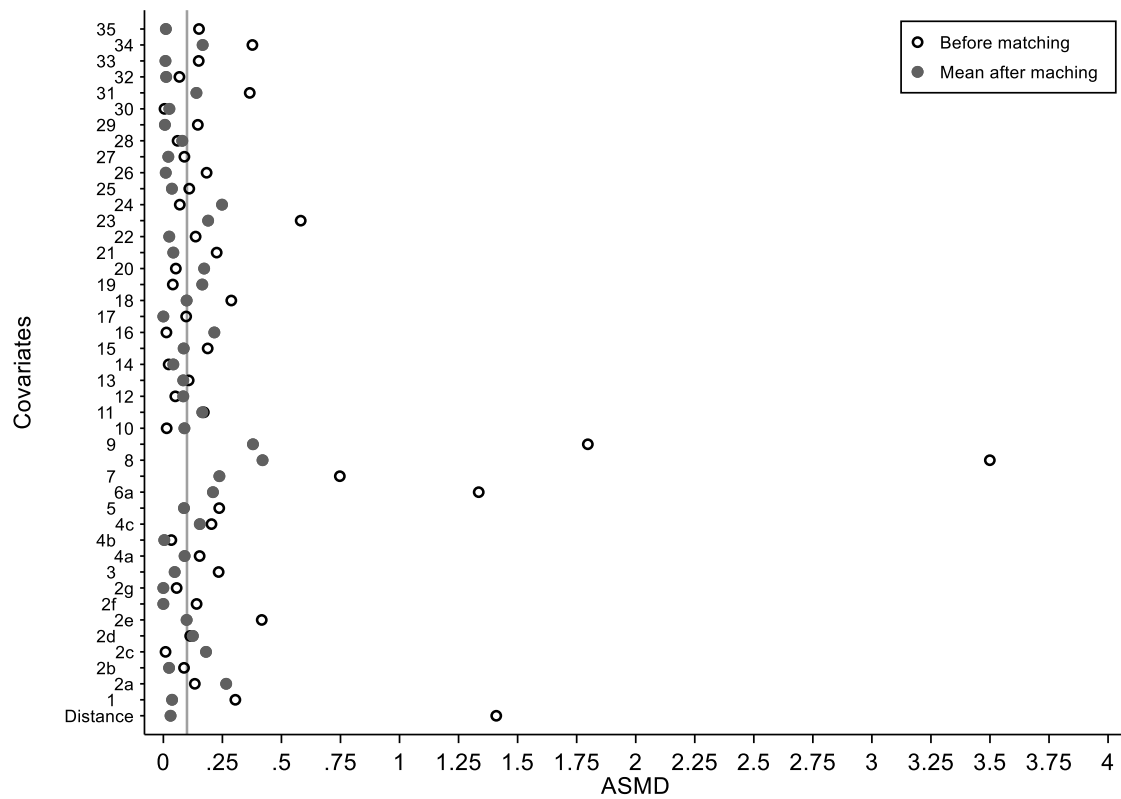
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## FIGURES

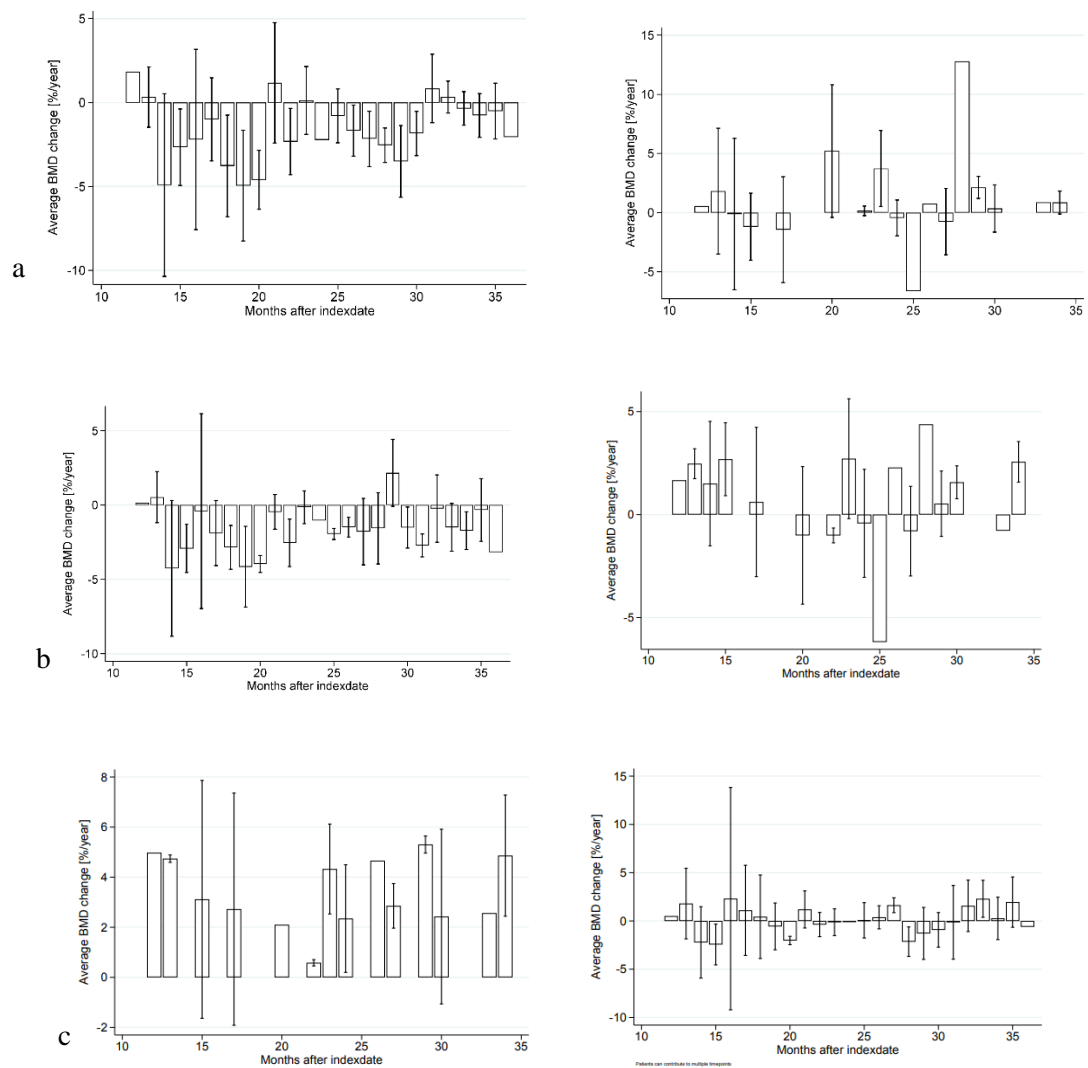


**Fig 1** Construction of treatment episodes based on prescription data



**Fig 2** Absolute standardised mean difference (ASMD) of each covariate included in the propensity score matching for renal and safety outcomes before (○) and after (●) matching

1 age, 2a Charlson score of 0, 2b Charlson score of 1, 2c Charlson score of 2, 2d Charlson score of 3, 2e Charlson score of 4, 2f Charlson score of 5, 2g Charlson score of 6+, 3 eGFR 4a two prescriptions in past year, 4b three prescriptions in past year, 4c four or more prescriptions in past year, 5 body mass index, 6a two hospital visits, 7 history of hip fracture, 8 history of non-osteoporotic fracture, 9 history of non-hip osteoporotic fracture, 10 diagnosis of rheumatoid arthritis, 11 uncomplicated diabetes, 12 complicated diabetes, 13 dementia, 14 cerebrovascular disease, 15 peripheral vascular disease, 16 hypertension, 17 mild liver disease, 18 renal disease, 19 chronic heart failure, 20 chronic obstructive pulmonary disease, 21 cancer, 22 treatment with oral contraceptives, 23 anti-osteoporotics, 24 defined daily dose of systemic steroids, 25 treatment with anticoagulants, 26 proton pump inhibitors, 27 anti-anxiety medication, 28 SSRIs, 29 statins, 30 ACE inhibitors, 31 antiepileptics, 32 diuretics, 33 beta blockers, 34 antidiabetics 35 antihypertensives. ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; SSRI, selective serotonin reuptake inhibitor.



**Fig 3** Average bone mineral density (BMD) change per month for bisphosphonate users (left) and non-users (right) in the femoral neck (a), hip (b), and spine (c).

## TABLES

**Table 1** Baseline characteristics for eligible and included bisphosphonate users

Characteristic	Eligible	Included
Unique patients (N)	270	71
eGFR, mean (SD)	37.2 (7.2)	37.9 (8.0)
Dead within 3 years of first bisphosphonate	35 (13.0%)	0 (0.0%)
Age, median (IQR)	82 (76-87)	79 (70-83)
Gender, female N (%)	268 (99.3%)	71 (100.0%)
<b>Index BMD<sup>a</sup>, mean (SD)</b>		
Total hip	0.657 (0.123)	0.678 (0.117)
Femoral neck	0.551 (0.110)	0.560 (0.106)
Spine	0.791 (0.165)	0.782 (0.166)
<b>Fractures, N (%)</b>		
Hip	21 (7.8%)	5 (7.0%)
Non-hip other	21 (7.8%)	5 (7.0%)
Non-hip osteoporotic	28 (10.4%)	6 (8.5%)
<b>Charlson score, N (%)</b>		
0	142 (52.6%)	39 (54.9%)
1	64 (23.7%)	18 (25.4%)
2	29 (10.7%)	7 (9.9%)
≥ 3	35 (13.0%)	7 (9.9%)
<b>Concomitant drugs, N (%)</b>		
Systemic corticosteroids	98 (36.3%)	29 (40.8%)
Anticoagulants	163 (60.4%)	35 (49.3%)
Statins	106 (39.3%)	30 (42.3%)
Antidiabetics	38 (14.1%)	7 (9.9%)
Antihypertensives	198 (73.3%)	58 (81.7%)

<sup>a</sup> up to one year before index date

BMD, bone mineral density; discontin., discontinued; eGFR, estimated glomerular filtration rate; IQR, interquartile range; OP, osteoporotic; SD, standard deviation

**Table 2** Baseline characteristics according to bisphosphonate use

	<b>Before matching</b>		<b>After matching</b>	
	Users	Non-users	Users	Non-users
<b>Patients (N)</b>	71	1,492 <sup>a</sup>	40	142
eGFR, mean (SD)	37.9 (8.0)	36.1 (7.7)	37.1 (9.1)	38.0 (6.7)
Age, median (IQR)	79 (70-83)	80 (76-85)	79 (75-82)	79 (73-84)
<b>Gender, N (%)</b>				
Females	71 (100%)	1,492 (100%)	40 (100.0%)	142 (100.0%)
Males	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Bone mineral density</b>				
Total hip	0.678 (0.117)	0.754 (0.144)	0.663 (0.119)	0.738 (0.134)
Femoral neck	0.560 (0.106)	0.627 (0.121)	0.547 (0.104)	0.617 (0.104)
Spine	0.782 (0.166)	0.877 (0.171)	0.806 (0.146)	0.881 (0.176)
<b>Fractures, N (%)</b>				
Hip	5 (7.0%)	28 (1.9%)	5 (12.5%)	(n < 5)
Non-hip other	5 (7.0%)	99 (6.6%)	(n < 5)	(n < 5)
Non-hip osteoporotic	6 (8.5%)	89 (6.0%)	(n < 5)	6 (4.2%)
<b>Charlson score, N (%)</b>				
0	39 (54.9%)	778 (52.1%)	27 (67.5%)	95 (66.9%)
1	18 (25.4%)	322 (21.6%)	8 (20.0%)	23 (16.2%)
2	7 (9.9%)	213 (14.3%)	(n < 5)	9 (6.3%)
≥ 3	7 (9.9%)	179 (12.0%)	(n < 5)	8 (5.6%)
<b>Drugs, N (%)</b>				
Systemic corticosteroids	29 (40.8%)	493 (33.0%)	11 (27.5%)	51 (35.9%)
Anticoagulants	35 (49.3%)	818 (54.8%)	18 (45.0%)	61 (43.0%)
Statins	30 (42.3%)	522 (35.0%)	17 (42.5%)	51 (35.9%)
Antidiabetics	7 (9.9%)	316 (21.2%)	5 (12.5%)	26 (18.3%)
Antihypertensives	58 (81.7%)	1,331 (75.8%)	32 (80.0%)	112 (78.9%)
<b>Additional diagnoses, N (%)</b>				
Diabetes (uncomplicated)	5 (7.0%)	171 (11.5%)	(n < 5)	16 (11.3%)
Diabetes with complications	(n < 5)	30 (2.0%)	(n < 5)	(n < 5)
Dementia	(n < 5)	40 (2.7%)	(n < 5)	(n < 5)
Cardiovascular disease	(n < 5)	17 (1.1%)	0 (0%)	(n < 5)
Hypertension	16 (22.5%)	328 (22.0%)	7 (17.5%)	26 (18.3%)
COPD	8 (11.3%)	143 (9.6%)	(n < 5)	14 (9.9%)
Heart failure	17 (23.9%)	383 (25.7%)	8 (20.0%)	27 (19.0%)
Renal transplant	0 (0.0%)	6 (0.4%)	0 (0%)	0 (0%)
Renal dialysis	0 (0.0%)	20 (1.3%)	0 (0%)	0 (0%)

<sup>a</sup> 1,492 episodes in 206 unique patients.

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation

**Table 3** Results of the analysis of bone mineral density (BMD) changes in participants exposed and unexposed to bisphosphonates.

	Analysis	Non-user		User		Mean difference (95% CI)
		N	BMD change	N	BMD change	
Femoral neck	PS-matched	142	-1.59	40	1.07	<b>2.65 (1.32, 3.99)</b>
	Multivariable	1492	-1.67	71	0.63	<b>2.14 (1.22, 3.05)</b>
	PS-adjusted	1492	-1.67	71	0.63	<b>2.15 (0.97, 3.34)</b>
Spine	PS matched	142	0.34	40	3.36	<b>3.01 (1.74, 4.28)</b>
	Multivariable	1492	0.65	71	3.98	<b>2.14 (1.22, 3.05)</b>
	PS-adjusted	1492	0.65	71	3.98	<b>2.87 (1.62, 4.12)</b>
Total hip	PS-matched	142	-1.16	40	0.95	<b>2.12 (0.98, 3.25)</b>
	Multivariable	1492	-2.14	71	0.82	<b>2.29 (1.46, 3.11)</b>
	PS-adjusted	1492	-2.14	71	0.82	<b>1.91 (0.82, 3.00)</b>

PS, propensity score